Amendments to the Specification:

Please replace the paragraph beginning at page 1, line 9, with the following replacement paragraph.

This application is the US national phase of PCT/US99/11179, filed May 20, 1999, which is a non-provisional of and ~~This application~~ derives priority from USSN 60/086,570 filed May 20, 1998, which is incorporated by reference in its entirety for all purposes.

Please replace the paragraph beginning on page 4, line 14, with the following replacement paragraph.

Some humanized antibodies are a humanized form of mouse antibody ~~VTml-1~~ VTml.1, the mouse antibody being characterized by a light chain variable region shown in Fig. 1B and a heavy chain variable region shown in Fig. 1A.

Please replace the paragraph beginning on page 4, line 18, with the following replacement paragraph.

The invention further provides antibodies that ~~competes~~ compete with mouse antibody ~~VTml-1~~ VTml.1 for specific binding to VT2 and/or VT2 variant.

Please replace the paragraph beginning on page 4, line 21, with the following replacement paragraph.

Some of the humanized antibodies, as described above, comprise complementarity determining regions from the mouse ~~VTml-1~~ VTml.1 antibody and heavy and light chain variable region frameworks from the human GF4 antibody heavy and light chain frameworks, provided that at least one position selected from the group consisting of L49, H29, H30, H49 and H98, is occupied by the amino acid present in the equivalent position of the mouse ~~VTml-1~~ VTml.1 antibody heavy or light chain variable region framework. Such humanized antibodies

specifically ~~binds~~ bind to verotoxin II with an affinity constant between10^7 M^{-1} and three, five or ten-fold the affinity of the mouse ~~VTml-1~~ VTml.1 antibody.

Please replace the paragraph beginning on page 4, line 33, with the following replacement paragraph.

In some humanized antibodies described in the previous paragraph, each position selected from the group consisting of L49, H29, H30, H49 and H98 is occupied by the amino acid present in the equivalent position of the mouse ~~VTml-1~~ VTml.1 antibody heavy or light chain variable region framework.

Please replace the paragraph beginning on page 5, line 21, with the following replacement paragraph.

Some humanized antibodies comprise a humanized heavy chain having at least 85% identity with the humanized heavy chain shown in Fig. 2A and a humanized light chain having at least 85% sequence identity with the humanized light chain showing in Fig. 2B, provided that at least one position selected from the group consisting of L49, H29, H30, H49 and H98, is occupied by the amino acid present in the equivalent position of the mouse ~~VTml-1~~ VTml.1 antibody heavy or light chain variable region framework.

Please replace the paragraph beginning on page 6, line 3, with the following replacement paragraph.

The invention further provides methods of producing humanized ~~VTml-1~~ VTml.1 antibody. Such methods comprise culturing a cell line, which encodes heavy and light chain chains of any of the antibodies described above, whereby the humanized antibody is expressed; and recovering the humanized antibody expressed by the cell line. Some such methods further comprise mixing the antibody with a pharmaceutically acceptable carrier to produce a pharmaceutical composition.

Please replace the paragraph beginning on page 6, line 21, with the following replacement paragraph.

The invention further provides methods of treating a patient suffering or at risk of toxic effects from a verotoxin, comprising administering to the patient an effective dosage of a human or humanized antibody that specifically binds to verotoxin II and/or verotoxin II variant. In some such methods, the antibody competes with mouse antibody ~~VTml-1~~ VTml.1 for specific binding to verotoxin II or verotoxin II variant. In some such methods, the humanized antibody specifically binds to VT2 and/or VT2 variant. In some such methods, the humanized antibody specifically binds to the B subunit of VT2 and/or VT2 variant. In some such methods, the humanized antibody specifically binds to VT2 and/or VT2 variant and neutralizes VT2 and/or VT2 variant. In some such methods, the humanized antibody specifically binds to the B subunit of VT2 and/or the B subunit of VT2 variant and neutralizes VT2 and/or VT2 variant. In some such methods, the antibody is a humanized antibody, which is a humanized form of the mouse ~~VTml-1~~ VTml.1 antibody. In some such methods, the antibody is a humanized antibody comprising a heavy chain variable region shown in Fig. 2A and a light chain variable region shown in Fig. 2B. In some such methods, the patient is infected with verotoxin producing *E. coli* and the antibody is administered therapeutically. In some such methods, the patient is at risk of infection by verotoxin producing *E. coli* and the antibody is administered prophylactically. Some such methods further comprise monitoring the patient for recovery from the toxic effects of verotoxin II or verotoxin II variant.

Please replace the paragraph beginning on page 7, line 13, with the following replacement paragraph.

In a further aspect, the invention provides a cell ~~lines~~ line which produces any of the above described antibodies.

Please replace the paragraph beginning on page 7, line 15, with the following replacement paragraph.

The present invention provides novel compositions useful, for example, in the treatment of Verotoxin ~~producing~~ Producing *E. coli* (VTEC) infection and Hemolytic Uremic Syndrome (HUS), the compositions containing humanized immunoglobulins specifically capable of binding to the B subunit of VT2 antigen and of neutralizing VT2 and VT2 variants. The immunoglobulins can have two pairs of light chain/heavy chain complexes, at least one chain comprising one or more mouse complementarity determining regions functionally joined to human framework region segments. For example, mouse complementarity determining regions, with or without additional naturally associated mouse amino acid residues, can be introduced into human framework regions to produce humanized immunoglobulins capable of binding to the antigen at affinity levels stronger than about 10^7 M^{-1}. These humanized immunoglobulins will also be capable of blocking the binding of the CDR-donating mouse monoclonal antibody to VT2.

Please replace the paragraph beginning on page 8, line 7, with the following replacement paragraph.

The humanized immunoglobulins may be utilized in substantially pure form in treating potentially toxic outcomes from VT2 or VT2V such as those produced during Verotoxin ~~producing~~ Producing *E. coli* (VTEC) infection and Hemolytic Uremic Syndrome (HUS). The humanized immunoglobulins or their complexes can be prepared in a pharmaceutically accepted dosage form, which will vary depending on the mode of administration.

Please replace the paragraph beginning on page 8, line 32, with the following replacement paragraph.

Figure 4. Competitive binding of MuVTml.l and HuVTml.1 antibodies to *E. coli* ~~verotoxin~~ Verotoxin II (VT2). Increasing concentrations of competitor antibody were incubated with coated VT2 in the presence of biotinylated tracer MuVTml.1.

Please replace the paragraph beginning on page 9, line 7, with the following replacement paragraph.

Figure 6. Identification of ~~Recognized~~ recognized antigen (the B subunit of VT2) of HuVTml.l.

Please replace the paragraph beginning on page 12, line 10, with the following replacement paragraph.

In accordance with the present invention, humanized immunoglobulins specifically reactive with the B subunit of VT2 are provided. These immunoglobulins, which have binding affinities to the B subunit of VT2 of at least about10^{-7} M^{-1} to10^{10} M^{-1}, and preferably10^{8} M^{-1} to $10^{10}M^{-1}$or stronger, are capable of, *e.g.*, neutralizing the toxicity of VT2 and VT2V (the VT2 antigens). The humanized immunoglobulins will have a human framework and will have one or more complementarity determining regions (CDR's) from an immunoglobulin, typically a mouse immunoglobulin, specifically reactive with VT2 antigens. In a preferred embodiment, one or more of the CDR's will come from the MuVTml.1 antibody. Thus, the immunoglobulins of the present invention, which can be produced economically in large quantities, find use, for example, in the treatment of the toxic outcomes from Verotoxin ~~producing~~ Producing *E. coli* (VTEC) infection and Hemolytic Uremic Syndrome (HUS) in human patients by a variety of techniques.

Please replace the paragraph beginning on page 13, line 22, with the following replacement paragraph.

As used herein, the term "immunoglobulin" refers to a protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as the myriad immunoglobulin variable region genes. The immunoglobulins may exist in a variety of forms besides antibodies; including, for example, Fv, Fab, and F $(ab')_2$- as well as bifunctional hybrid antibodies (*e.g.*, Lanzavecchia et al., Eur. J. Immunol. 17,105 (1987)) and in single chains (e.g., Huston et al., Proc. Natl. Acad. Sci. U. S. A., 85,58795883 (1988) and Bird et

al., Science 242,423-426 (1988), which are incorporated herein by reference). (*See*, generally, Hood et al., Immunology, Benjamin, N. Y.,2nd ed. (1984), Harlow and Lane, Antibodies. A Laboratory Manual, Cold Spring Harbor Laboratory (1988) and Hunkapiller and Hood, Nature, 323,15-16 (1986), which are incorporated herein by reference[[.]]).

Please replace the paragraph beginning on page 17, line 17, with the following replacement paragraph.

Human constant region DNA sequences can be isolated in accordance with well known procedures from a variety of human cells, but preferably immortalized B-cells (*see*, Kabat op. cit. and WP 87/02671). The CDR's for producing the immunoglobulins of the present invention will be similarly derived from monoclonal antibodies capable of binding to VT2 antigens and produced in any convenient mammalian source, including, mice, rats, rabbits, or other vertebrate capable of producing antibodies by well known methods. Suitable source cells for polynucleotide sequences and host cells for immunoglobulin expression and secretion can be obtained from a number of sources, such as American Type Culture Collection (Catalogue of Cell Lines and Hybridomas, Fifth edition (1985) ~~Rockville, Maryland,~~ 10801 University Boulevard, Manassas, VA, U.S.A., which is incorporated herein by reference.

Please replace the paragraph beginning on page 17, line 32, with the following replacement paragraph.

In addition to the humanized immunoglobulins specifically described herein, other "substantially homologous" modified immunoglobulins can be readily designed and manufactured utilizing various recombinant DNA techniques well known to those skilled in the art. For example, the framework regions can vary from the native sequences at the primary structure level by several amino acid substitutions, terminal and intermediate additions and deletions, and the like. Moreover, a variety of different human framework regions may be used singly or in combination as a basis for the humanized modifications of the present invention. In general, modifications of the genes may be readily accomplished by a variety of well-known

techniques, such as site-directed mutagenesis (see, Gillman and Smith, Gene 8, 81-97 (1979) and Roberts S. et al., Nature 328, 731-734 (1987), both of which are incorporated herein by reference.[[)]]

Please replace the paragraph beginning on page 21, line 1, with the following replacement paragraph.

The immunoglobulins of the present invention will typically find use individually in treating the toxic effects of ~~Verotoxinproducing~~ Verotoxin Producing *E.coli* (VTEC) infection and Hemolytic Uremic Syndrome (HUS) and/or in neutralizing VT2 antigens. By way of example but not limitation, some typical disease states suitable for treatment include hemorrhagic colitis locally in the gut, renal dysfunction, and brain damage.

Please replace the paragraph beginning on page 21, line 8, with the following replacement paragraph.

The humanized immunoglobulins and pharmaceutical compositions thereof of this invention are particularly useful for parenteral administration, *i.e.*, subcutaneously, intramuscularly or intravenously. The compositions for parenteral administration will commonly comprise a solution of the immunoglobulin or a cocktail thereof dissolved in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used, *e.g.*, water, buffered water, 0.4% saline, 0.3% glycine, 5% glucose, [[']]human albumin solution and the like. These solutions are sterile and generally free of particulate matter. These compositions may be sterilized by conventional, well-known sterilization techniques. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, tonicity agents, toxicity adjusting agents and the like, for example sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, sodium citrate, etc. The concentration of immunoglobulin in these formulations can vary widely, *i.e.*, from the less than about 0.5%, usually at least about 1% to as much a 15 or

20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., in accordance with the particular mode of administration selected.

Please replace the paragraph beginning on page 22, line 18, with the following replacement paragraph.

The compositions containing the present humanized immunoglobulins or a cocktail thereof can be administered for therapeutic or prophylactic treatments. In therapeutic application, compositions are administered to a patient already suffering from Verotoxin ~~producing~~ Producing *E. coli* (VTEC) infection and Hemolytic Uremic Syndrome (HUS), or other toxic manifestations from VT2 antigens, in an amount sufficient to cure or at least partially arrest the toxic syndrome and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose." In prophylactic applications, compositions are administered to patients at risk of infection in an amount sufficient to prevent or detectably inhibit such infection and/or toxic manifestation thereof due to VT2 antigens. Amounts effective for such uses depend upon the severity of the disease and the general state of the patient's own immune system, but generally range from 0.1 to 5 mg/kg of immunoglobulin per patient dose being commonly used. It must be kept in mind that the materials of this invention may generally be employed in serious disease states, that is life-threatening or potentially life-threatening situations. In such cases, in view of the minimization of extraneous substances and the lower probability of "foreign substance" rejections which are achieved by the present humanized immunoglobulins of this invention, it is possible and may be felt desirable by the treating physician to administer substantial excesses of these immunoglobulins.

Please replace the paragraph beginning on page 23, line 17, with the following replacement paragraph.

In particular embodiments, compositions comprising humanized immunoglobulin of the present invention may be used to detect VT2 antigens in Verotoxin ~~producing~~ Producing *E. coli* (VTEC) infection and Hemolytic Uremic Syndrome (HUS) and/or in other infections producing

VT2 or VT2V. Thus, a humanized immunoglobulin of the present invention, such as a humanized immunoglobulin that binds to the antigen determinant identified by the MuVTm1.1 antibody may be labeled and used to identify anatomic sites that contain significant concentrations of VT2 or VT2V. For example but not for limitation, one or more labeling moieties may be attached to the humanized immunoglobulin. Exemplary labeling moieties include, but are not limited to, radiopaque dyes, radiocontrast agents, fluorescent molecules, spin-labeled molecules, enzymes, or other labeling moieties of diagnostic value, particularly in radiologic or magnetic resonance imaging techniques.

Please replace the paragraph beginning on page 25, line 2, with the following replacement paragraph.

In another aspect of the invention, human antibodies that compete with mouse ~~VTml-1~~ VTml.1 for binding to verotoxin II or verotoxin II variant are provided.